REMARKS

Claims 29-31 are pending in this application.

The Examiner has rejected claims 29-31 under 35 U.S.C. 112 first paragraph on the basis that the specification while being enabling for treating diabetes complications, does not enable the prevention of diabetes related complications. Applicants respectfully traverse this rejection.

The Examiner states that the claims are broad enough to include prevention of any or all diseases including those yet to be discovered for which there is no pharmacological basis in the specification. Applicants respectfully disagree with this characterization. Claim 29 is limited to the complications of hyperglycemia, osteoporosis, hyperlipidemia, nephrotic syndrome or disorders related to endothelial cell division (see last 2 lines of the claim). The same is true for claims 30 and 31.

The data on pages 77, 79 and 80 show that the compounds of this invention lower triglycerides. The data on page 79 also shows that the compounds of this invention increase HDL and lower LDL and VLDL.

In addition the data in this application clearly shows that the compounds of this invention lower blood glucose levels. By lowering blood glucose levels, it is expected that diabetes can be prevented and thus the complications thereof can be prevented. If the compounds of this invention can be used to prevent diabetes, then it is understood that they would prevent complications of diabetes.

J. Clin . Investigation (1985), 75, 809-817; J. Clin. Investigation (1981), 68, 957-969; J. Clinical Endocrinology Metab. (1988) 66, 580-583 and also WO 95/21608; WO 95/07697; WO 95/35108 describe that impaired glucose tolerance and insulin resistance may leads to diabetes and thus complications of diabetes. By administering compounds of the present invention to those who are at risk of developing insulin resistance or impaired glucose tolerance and thus type II diabetes, it is possible to prevent or delay the onset of complications of diabetes described above which are related to insulin resistance or impaired glucose tolerance.

Support for these claims is found in the section titled Background of the

Invention. Copies WO 95/21608, WO 95/07697, WO 95/35108 and Messier, et al. Behavioral Brain Research, 75 (1996) p. 1-11 are attached. In addition, along with these references, attached are J. Clin. Invest (1985) 75:809-817; J. Clin. Invest. (1981) 68:957-969; J. Clin. Endocrinol. Metab. (1988) 66, 580-583 cited in the disclosure. The following references describe that impaired glucose tolerance and insulin resistance may lead to complications such as hypertension, atherosclerosis, myocardial intarction, cardiovascular impairment, nephropathy, neuropathy, coronary heart disease, stroke or peripheral vascular disease. By treating impaired glucose tolerance or insulin resistance by administering compounds according to this invention to those who are at risk for developing insulin glucose tolerance and thus type II diabetes, it is possible to prevent or delay the onset of the above diseases which are related to insulin resistance or impaired glucose tolerance.

1) Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition, pgs. 1496-1497.

> An almost pathognomic feature of diabetes mellitus is thickening of the capillary basement membranes and other vascular changes that occur during the course of the disease...These pathologic changes contribute to some of the major complications of diabetes, including premature atherosclerosis, interapillary glomerulosclerosis, retinopathy, neuropathy and ulceration and gangrene of the extremities...It has been hypothesized that the factor responsible for the development of most complications of diabetes in the prolonged exposure of tissues to elevated concentration of glucose.

2) Clifford Bailey, "Potential New Treatments for Type 2 Diabetes" Chemistry & Industry, January 19, 1998, pgs. 53-57.

> Type 2 (non-insulin-dependent) diabetes mellitus...is characterized by a raised blood glucose concentration (hyperglaemia)... The condition develops insidiously, and many cases pass unrecognized until the

appearance of long-term complications, particularly those affecting blood vessels. Atherosclerosis (fatty deposits in the walls of the major arteries) causes a two-to four-fold increase in the risk of coronary heart disease, strokes, and peripheral vascular disease. Damage to small vessels in the retina seriously impairs vision in 15-20% of patients; kidney disease (nephropathy) leads to renal failure in 5% of patients; and disorder of the nervous system (neuropathy) contribute to foot ulcers...

3) T. Antonucci et al. "Impaired Glucose Tolerance is Normalized by Treatment with the Thiazolidinedione Troglitazone" Diabetes Care, Vol. 20, No. 2, February 1997, pages 188-193.

...many [impaired glucose tolerance] IGT patients risk subsequent development of hypertension, atherosclerosis, myocardial infarction, and other cardiovascular impairment. Insulin resistance accompanies IGT, ...patients with both IGT and insulin resistance are at highest risk for cardiovascular complications. Furthermore, insulin resistance is associated with increased plasma insulin levels, which have also been implicated in cardiovascular morbidity.

4) Baillieres, Clin Endocrinol Metab 1993 Oct; 7(4):1063-78.

In this presentation an effort has been made to review the impact of resistance to insulin-mediated glucose uptake and/or hyperinsulinemia on various metabolic end points and clinical syndromes. Insulin resistance is present in the great majority of patients with states of glucose intolerance, but frank decompensation of glucose homoeostasis does not occur if individuals can maintain a state of compensatory hyperinsulinaemia. Although compensatory hyperinsulinaemia. Although compensatory hyperinsulinaemia may prevent the development of NIDDM in insulin-resistant individuals, there is substantial evidence that insulin resistance and/or hyperinslinaemia is associated with higher

plasma concentrations of triglyceride, uric acid and plasminogen activator inhibitor 1 and with lower HDL cholesterol concentrations. Resistance to insulin-mediated glucose uptake and/or hyperinsulinaemia have been shown to be associated with high blood pressure, microvascular angina and CHD. Thus, resistance to insulin-mediated glucose uptake is a common phenomenon, whch makes a major contribution to the actiology and clinical course of common and serious diseases. Based on the above considerations, it is difficult to over-emphasize the health-related implication of a defect in insulin-mediated glucose uptake.

5) J Am Soc Nephrol 2003 Feb;14(2):469-77.

This study examined the relationship of fasting serum glucose, insulin, C-peptide, glycosylated hemoglobin A (HbAlc), and Homeostasis Model Assessment (HOMA)-insulin resistance to risk of chronic kidney disease (CKD) among 6453 persons without diabetes (fasting glucose <126 mg/dl and not taking diabetes medication) who participated in the Third National Health and Nutrition Examination Survey and were aged 20 yr or older. Those finding combined with knowledge from previous studies suggest that the insulin resistance and concomitant hyperinsulinemia are presented in CKD patients without clinical diabetes. Further studies into the causality between insulin resistance and CKD are warranted.

6) MMW Fortschr Med. 2000, June 22, 142 (25); 42-4.

Hypertension alone can lead to chronic nephrosclerosis and in addition promote the progressive worsening of renal function in various forms of renal disease, such as diabetic nephropathy, glomerular nephritis or interstital nephritis. Thus, the treatment of chronic renal disease associated with reduced excretory function, requires not only general

measures and a low-protein diet, but also intensified anti-hypertension treatment with diuretics or beta blockers.

7) Kidney Int 2001 Jul;60(1): 14-30.

Peroxisome proliferator-activated receptors (PPARs): Novel therapeutic targets in renal disease. Peroxisome proliferator activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of ligand-dependent transcription factors. PPARs play an important role in the general transcriptional control of numerous cellular processes, including lipid metabolism, glucose homeostasis, cell cycle progression, cell differentiation, inflammation and extracellular matrix remodeling. PPARalpha primary regulates lipid metabolism and modulates inflammation. PPARalpha is the molecular target of the hypolipidemic fibrates including bezafibrate and clofibrate. PPARgamma is a key factor in adipogenesis and also plays an important role in insulin sensitivity, cell cycle regulation and cell differentiation. Antidiabetic thiazolidinediones (TXDs) such as troglitazone and rosiglitazone are specific ligands of PPARgamma, and this interaction is responsible for the insulin-sensitizing and hypoglycemic effect of these drugs. The kidney has been shown to differentially express all PPAR isoforms. PPARalpha is predominantly expressed in proximal tubules and medullary thick ascending limbs, while PPARgamma is expressed in medullary collecting ducts, pelvic urothelium and glomerular mesangial cells. PPARbeta is ubiquitously expressed at low levels in all segments of nephron. Accumulating data has begun to emerge suggesting physiological and pathophysiological roles of PPARs in several tissues including the kidney. The availability of PPAR-selective agonists and antagonists may provide a new approach to modulate the renal response to diseases including glomerulonephritis, glomerulosclerosis and diabetic nephropathy.

8) Bioorganic & Medicinal Chemistry Letters, 1996, Vol. 6, No. 17, 2121-2126.

Insulin resistance and associated hyperinsulinaemia are being implicated increasingly in the development of other metabolic disorders such as obesity, dyslipidaemias and hypertension.

9) J. Med. Chem. 1996, 39, 3897-3907.

Non-insulin-dependent diabetes mellitus (NIDDM) is a metabolic disorder leading to long-term organ complications such as neuropathy, nephropathy, retinopathy and premature atherosclerosis.

10) Use of PPAR agonists against endothelial cell activation (Biochem. Biophys. Res. Commun., 2002, May, 293(5), 1431-37.

Peroxisome proliferator-activated receptors (PPARs) regulate lipid and glucose metabolism and exert several vascular effects that may provide a dual benefit of these receptors on metabolic disorders and atherosclerotic vascular disease. Therefore investigated the effects of lipid-lowering PPARalpha-activators (fenofibrate, WY 14643) and antidiabetic PPARgamma-activators (troglitazone, ciglitazone) on this endothelial cell function. Both PPARalpha- and PPARgamma-activators significantly inhibited VEGF-induced migration of human umbilical vein endothelial cells (EC) in a concentration-dependent manner. VEGF-induced Akt phosphorylation was significantly inhibited by both PPARalpha- and gamma-activators. These results provide first evidence for the antimigratory effects of PPAR-activators in EC. By inhibiting EC migration PPAR-activators may protect the vasculature from pathological alterations associated with metabolic disorders.

11) Use of PPAR agonists against osteoporosis (Nippon Rinshó, 2000, 58(2), 456-60; Br. J. Pharmacol., 2000, 130(3), 495 504).

> Thiazolidinedione (TZD), a new class of anti-diabetic agents, is known promote adipocytic differentiation by activating peroxisome proliferator-activated receptor-gamma (PPAR gamma). In the bone marrow, osteoblasts and adipocytes are derived from common mesenchymal stem cells or stromal cells, which also play crucial roles in the generation of osteoclasts from their progenitor hematopoietic cells. Recent in vitro studies demonstrated that TZDs promote adipocytic differentiation of the stromal cells. However, whether or not this affects osteoblastic differentiation is unclear. On the other hand, TZDs clearly inhibit osteoclast-like cell formation and bone resorption in vitro. These results indicate that TZDs have direct effects on bone cells. However, little is known about their in vivo effects on bone. Our recent study demonstrated that troglitazone, a TZD, decreased bone resorption markers before it affected glycemic indices in type2 diabetics, suggesting TZDs affects bone in vivo and may be beneficial for bone health in type2 diabetics.

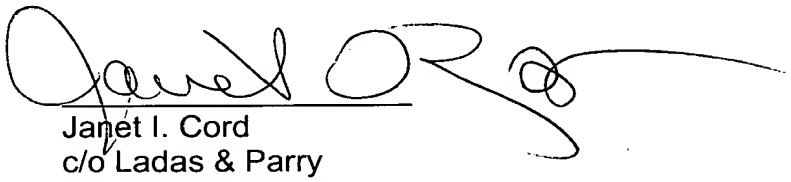
Applicants disagree with the Examiner's characterization that the specification provides no guidance or direction, as to how one would use the instant compound to prevent all or any disorders of diabetes. As stated above the complications are limited to hyperglcemia, osteoporosis, hyperlipidemia, nephrotic syndrome or disorders related to endothelial cell division. The Examiner acknowledges that there are working Examples to show how the instant compound could be used to prevent disorders wherein PPAR receptors implicated as a causative agent or HMG CoA Reductase is implicated. There are also examples in the specification showing the fact that compounds of this invention reduce blood glucose i.e. the lead to prevention or mitigation of diabetes.

Based on the above, it is clear that claims 29-31 are enabled.

Therefore, it is respectfully requested that this rejection be withdrawn.

Applicants submit that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted



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